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Bell's palsy and SARS-CoV-2 vaccines

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In light of the ongoing pandemic, development of vaccines to protect against SARS-CoV-2 infection and COVID-19 disease is an important public health priority. As of February 2021, two SARS-CoV-2 vaccines have received emergency use authorisation by the US Food and Drug Administration (FDA), both of which use mRNA technology. While the safety data are reassuring, phase 3 studies of both vaccines demonstrate an imbalance of cases of Bell's palsy in the vaccine groups compared with the placebo groups. This Comment has three purposes: to briefly review the literature on the association of Bell's palsy with vaccination, and vaccination for respiratory viruses such as influenza in particular, to consider biological mechanisms that might explain observed associations, and to reconsider statistical and epidemiological evidence from the reported safety data of the SARS-CoV-2 vaccine trials.

Associations between influenza vaccines and Bell's palsy have been studied extensively (table). Elevated incidence of Bell's palsy among recipients of an inactivated intranasal influenza vaccine was reported in a study conducted in 2000–01.[1] Since this vaccine contained the *Escherichia coli* heat-labile toxin as a mucosal adjuvant, which undergoes retrograde neuronal uptake, it was suspected that heat-labile toxin could affect the seventh cranial nerve through

	Vaccine type	Study design and population	Study period	Summary of the results
Inactivated intranasal influenza vaccine[1]	Virosomal subunit vaccine	A matched case-control study and case-series among patients with Bell's palsy (≥18 years of age)	2000–01	During the 91-day exposure period, compared with controls, recipients of the vaccine had an adjusted odds ratio for Bell's palsy of 84·0 (95% CI, 20·1–351·9)
Parenteral inactivated seasonal influenza vaccine[2]	Protein-based split vaccine	Review of adverse events reported to VAERS	1991–2001	Proportional reporting ratio of Bell's palsy after influenza vaccine: 3·78 (95% CI not provided)
Monovalent pandemic H1N1 influenza vaccine[3]	Split virion adjuvanted with AS03	Retrospective cohort study among 1 024 019 individuals vaccinated with pandemic influenza vaccine	2009–10	Increased incidence of Bell's palsy compared with unvaccinated people, with a hazard ratio of 1·25 (95% CI, 1·06–1·48)
Monovalent pandemic H1N1 influenza vaccine[4]	Two protein-based vaccines: adjuvanted with MF59, or without adjuvant	Review of adverse events reported to NADRRS, Taiwan	2009–10	Increased risk for Bell's palsy 0–42 days post-vaccination; estimated-to-expected ratio of 1·48 (95% CI, 1·11–1·98)
Quadrivalent meningococcal conjugate vaccine[5]	Protein vaccine conjugated to a carrier protein	Self-controlled case-series analysis among 48 899 individuals immunized with meningococcal vaccine (11–21 years of age)	2011–13	Increased relative incidence for Bell's palsy in participants receiving concomitant vaccines (5·0, 95% CI, 1·4–17·8)

VAERS=US Food and Drug Administration's Vaccines and Related Biologic Products Advisory Committee. NADRRS=National Adverse Drug Reaction Reporting System.

Table: **Summary of studies reporting an association between vaccination and Bell's palsy**

such an interaction. Potential signs of Bell's palsy have been reported following parenteral seasonal influenza vaccinations,[2] and influenza H1N1 monovalent pandemic vaccinations.[3,4] However, the association between parenteral influenza vaccines and Bell's palsy was not reproducible in other studies.

A meningococcal conjugate vaccine showed a significant association with Bell's palsy when administered simultaneously with other vaccines such as influenza, human papillomavirus, or diphtheria-tetanus-pertussis vaccines.[5] A similar study did not detect a significantly increased risk, even though more than half of study participants received meningococcal vaccine simultaneously with other vaccines.[6] Other vaccines studied have been reported to have no significant association with Bell's palsy.

One theory suggests vaccines could be associated with autoimmune phenomenon, which is thought to occur via either mimicry of host molecules by the vaccinal antigen or bystander activation of dormant autoreactive T-cells.[7] Such theorised associations have not withstood close scrutiny. The SARS-CoV-2 vaccines do not contain an exogenous adjuvant, but discussion between members of the FDA's Vaccines and Related Biologic Products Advisory Committee and a sponsor (Pfizer) raised the possibility that the vaccine might induce innate immune activation from a combined effect of mRNA and lipids, potentially including interferon production. Such interferon production could transiently break peripheral tolerance, a hypothetical phenomenon invoked in several case reports.[8,9]

We conclude with a consideration of the statistical and epidemiological implications of reported safety data of the SARS-CoV-2 vaccine trials. Publicly available data from the Pfizer-BioNTech and Moderna vaccine trials suggest an imbalance in the incidence of Bell's palsy following vaccination compared with the placebo arm of each trial. Combining data from both trials, among nearly 40 000 vaccine arm participants, there were seven Bell's palsy cases compared with one Bell's palsy case among placebo arm participants. This estimated rate ratio of roughly 7·0, suggests vaccination might be associated with Bell's palsy (p=0·07).

Media reports have stated that the incidence of Bell's palsy among participants of the Pfizer-BioNTech and Moderna vaccine trials is comparable to that observed in the general population. The FDA briefing on the Pfizer-BioNTech trial stated "observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population", although this statement was removed from the subsequent FDA briefing on the Moderna trial. However, this reporting is based on a misconception, driven by a subtle distinction between rates and proportions, that has persisted in the lay media. The estimated incidence rate of Bell's palsy in the general population ranges from 15 to 30 cases per 100 000 person-years. Since the 40 000 vaccine arm participants were followed for a median of 2 months, the combined safety population receiving vaccine across the two trials represents roughly 6700 person-years of observation time for an expected incidence of Bell's palsy of one to two cases, in line with the single observed case in the combined placebo arms. Therefore, the observed incidence of Bell's palsy in the vaccine arms is between 3·5-times and 7-times higher than would be expected in the general population. This finding signals a potential safety phenomenon and suggests inaccurate reporting of basic epidemiological context to the public.

Overall, both passive and active surveillance systems will be important to ensure vaccine safety. While we call for robust surveillance for potential mRNA vaccine-associated Bell's palsy, we also note that Bell's palsy usually self-resolves and we feel the available coronavirus mRNA vaccines offer a substantial net benefit to public health.

OL has patents pending on several vaccine adjuvants. AO and EN declare no competing interests.

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